



## Journal of Toxicology and Environmental Health, Part B

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/uteb20>

### Recent Advances in Research on Radiofrequency Fields and Health: 2001-2003

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Available online: 09 Jul 2007

To cite this article: Daniel Krewski, Barry W. Glickman, Riadh W. Y. Habash, Brian Habbick, W. Gregory Lotz, Rosemonde Mandeville, Frank S. Prato, Tarek Salem & Donald F. Weaver (2007): Recent Advances in Research on Radiofrequency Fields and Health: 2001-2003, *Journal of Toxicology and Environmental Health, Part B*, 10:4, 287-318

To link to this article: <http://dx.doi.org/10.1080/15287390600974973>

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## RECENT ADVANCES IN RESEARCH ON RADIOFREQUENCY FIELDS AND HEALTH: 2001–2003

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The widespread use of wireless telecommunications devices, particularly mobile phones, has resulted in increased human exposure to radiofrequency (RF) fields. Although national and international agencies have established safety guidelines for exposure to RF fields, concerns remain about the potential for adverse health outcomes to occur in relation to RF field exposure. The extensive literature on RF fields and health has been reviewed by a number of authorities, including the Royal Society of Canada (1999), the European Commission's Scientific Committee on Toxicity, Ecotoxicity, and the Environment (CSTEE, 2001), the British Medical Association (2001), the Swedish Radiation Protection Authority (Boice & McLaughlin, 2002), and the Health Council of the Netherlands (2002). This report provides an update on recent research results on the potential health risks of RF fields since the publication of the Royal Society of Canada report in 1999 (See Krewski et al., 2001a) and our previous 2001 update (Krewski et al., 2001b), covering the period 2001–2003. The present report examines new data on dosimetry and exposure assessment, biological effects such as enzyme induction, and toxicological effects, including genotoxicity, carcinogenicity, and testicular and reproductive outcomes. Epidemiological studies of mobile phone users and occupationally exposed populations are examined, along with human and animal studies of neurological and behavioral effects. All of the authoritative reviews completed within the last 2 yr have concluded that there is no clear evidence of adverse health effects associated with RF fields. However, following a recent review of nine epidemiological studies of mobile phones and cancer, Kundi et al. (2004) concluded that the possibility of an enhanced cancer risk cannot be excluded. These same reviews support the need for further research to clarify the possible associations between RF fields and adverse health outcomes that have appeared in some reports. The results of the ongoing World Health Organization (WHO) study of mobile phones will provide important new information in this regard.

The use of radiofrequency (RF) field-emitting devices such as mobile phones, microwave ovens and RF heaters, base stations, radar installations, and telecommunications and broadcast facilities has led to widespread human exposure to RF fields. As defined by the Institute of Electrical and Electronics Engineers (IEEE), RF is a band in the electromagnetic (EM) spectrum that lies in the frequency range of 3 kHz to 300 GHz. Microwave (MW) radiation is usually considered a subset of RF, which occupies the spectral region between 300 GHz to 300 MHz, while RF includes 300 MHz to 3 kHz. Since they have similar characteristics, RF and MW are recognized together, and referred to as RF throughout this article.

The remarkable growth of the telecommunication industry, especially mobile phones and base stations, has raised public concerns about possible associations between RF fields and adverse health outcomes, including cancer. To date, there are limited epidemiological data on the potential health risks associated with the use of mobile phones, which represent an important

This article represents an update of the original report of the Royal Society of Canada Expert Panel on the Potential Health Risks of Radiofrequency Fields, prepared by the Royal Society of Canada for Health Canada in 1999. We are grateful to the referees and the editor for many helpful comments on the original draft of this paper. D. Krewski is the NSERC/SSHRC/McLaughlin Chair in Population Health Risk Assessment at the University of Ottawa.

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source of exposure to RF fields (Kundi et al., 2004). As more products and services are developed and used in everyday applications, the potential for human exposure to RF fields is likely to increase, leading to continued public concerns about the potential health effects of such exposures.

The Royal Society of Canada's Expert Panel on Potential Health Risks from Wireless Telecommunication Devices conducted a detailed review of potential health risks of RF fields from wireless telecommunication devices (Royal Society of Canada, 1999; Krewski et al., 2001a). Subsequent research reported in the literature during the period 1999–2000 was then reviewed by Krewski et al. (2001b). This article is a continuation of the effort to review the literature on RF fields and health, specifically for the period 2001–2003.

## DOSIMETRY AND EXPOSURE ASSESSMENT

Dosimetry involves measuring the intensity of radiation emitted by a particular source, and includes the evaluation of both incident and internal fields. Internal fields and currents are responsible for interactions with living systems, regardless of whether these interactions are thermal or non-thermal. Internal and incident EM fields can be quite different, depending on (1) size and shape of the object, (2) electrical properties of the object, (3) orientation of the object with respect to incident fields, and (4) operating frequency.

Dosimetry involves the measurement or determination by calculation of the internal fields, induced current density, or specific absorption rate (SAR) distributions in objects like models (phantoms), animals, humans, or even parts of human body exposed to RF fields (Durney & Christensen, 1999). Because of the complexity and nonhomogeneous character of biological tissues, it is difficult to fully characterize the propagation of RF fields in human body.

### Mobile Phones

A mobile handset represents a significant source of RF field exposure, because of the presence of the phone-transmitting antenna close to head, neck, and hand of the user. Model-based predictions of the SAR associated with mobile phones are now required to comply with established exposure guidelines (1.6 W/kg or 2 W/kg) for the head and neck area. Mobile phone manufacturers are continually interested in reducing SAR as much as possible, not only to reduce exposure to RF fields but also to increase the battery life.

The local peak SAR levels inside the human head differ depending on many factors, including antenna characteristics, distance of the object from the source of radiation, effect of the hand holding the handset, and the structural accuracy and resolution of the head model. A number of dosimetric studies have been performed for calculating or measuring power absorbed in phantoms simulating human heads exposed to RF fields. Recently, Van de Kamer and Lagendijk (2002) calculated SAR from dipole antennas radiating 250 mW at 900 MHz. Some SAR values exceeded the limits commonly called "maximum permissible exposure" (MPE) values, while other values were below the MPE values. Moneda et al. (2003) verified by the means of numerical calculation that the higher the frequency the more superficial is the absorption. The numerical application manifests that the eyes, despite their small volume, absorb considerable amounts of the incident RF field, especially when the antenna is in front of the head, which is the most typical configuration related to use of mobile phones due to new applications such as short message services (SMS) and the Internet. Another important issue that was raised by the authors is the enhancement of the "hot-spot" region (significantly heating of areas from 1 cm to several cm due to relatively more intense RF radiation), which exists near the center of the brain due to the phenomenon of "resonance." This region covers mobile phone frequency range 300 MHz–3 GHz and the human head usually resonates at about 1 GHz depending on the shape of the skull, electrical characteristics of the brain, and the level of its water content.

To calculate temperature rise in the human head exposed to RF fields at 1.5 GHz at a density of 1 mW/cm<sup>2</sup>, Yano et al. (2001) developed a realistic adult head model and an infant size model by reducing the adult model. In the adult model, the maximum rise of temperature was reached in

the eyeballs ( $0.07^{\circ}\text{C}$ ), while in the infant model, the maximum rise of temperature occurred in the muscle ( $0.0058^{\circ}\text{C}$ ). The tissue average temperature rise was higher in the infant model than in the adult model except for the eyeballs. In particular, the average value of the temperature rise in the brain tissue was lower than the peak value by almost one order of magnitude and was three times higher than the average value in the adult. The reported results were attributed to the hot spots of SAR as a heat source generated inside the head.

The controversy on the dosimetry in children's heads for mobile phones is still inconsistent. Gandhi and Kang (2002) reported a considerable increase of the spatial SAR in children's heads, while Schoenborn et al. (1998) claimed that there was not a significant difference in the SAR between children and adults. Wang and Fujiwara (2003) developed two kinds of children's models from a Japanese adult head model. Using the children's head models, they calculated the local peak SAR under the same conditions as those previously employed by Gandhi and Kang (2002) and Schoenborn et al. (1998). Compared to the local peak SAR in the adult head model, they found a considerable increase in the children's heads when they fixed the output power of the monopole-type antenna, but no significant differences when they fixed the effective current of the dipole-type antenna. Their finding suggests that the contradictory conclusions drawn by Gandhi and Kang (2002) and Schoenborn et al. (1998) may be due to the different conditions in their numerical peak SAR calculations.

### Base Stations

The rapid growth of the cellular telecommunications industry has resulted in the installation of large networks of base transceiver stations (BTSs), which may be mounted on freestanding towers, rooftops, or the sides of buildings. Measurements near typical BTSs have mostly shown that exposure levels are well within the widely promulgated guidelines (Silvi et al., 2001; Anglesio et al., 2001; Cooper et al., 2002).

A report by the Advisory Group on Nonionizing Radiation of the National Radiological Protection Board (NRPB, 2001) giving advice on possible health effects of terrestrial trunked radio (TETRA) concluded that "Although areas of uncertainty remain about the biological effects of low level RF radiation in general, including modulated signals, current evidence suggests that it is unlikely that the special features of the signals from TETRA mobile terminals and repeaters pose a hazard to health." In an expert group report to the Director General of Health of France, Zmirou (2001) noted that personal exposures in the vicinity of base stations were low, and stated that "in view of the exposure levels observed, the expert group does not back the hypothesis that there is a health risk for populations living in the vicinity of base stations."

In summary, the many expert group statements on the issue of exposure to radiation from BTSs conclude that there is almost no evidence as a basis for a decision. In the light of this fact, these statements go a little bit far in expressing that there is no health risk. Most expert groups have started from the implicit assumption that exposure from BTSs is much lower than exposure to mobile phones and assuming that exposure duration (exposure to BTS signals may continue for 24 hours per day) plays no decisive role. However, it is possible that protracted exposure causes more pronounced effects than short exposures of high intensity, and there are examples (e.g. noise) of qualitatively different effects of low and high exposures. Hence at the moment, there is no evidence-based decision possible and the arguments of many panels are weak.

### Environmental Levels

Hondou (2002) found that when hundreds of mobile phones emit radiation, their total power is comparable to a microwave oven or a satellite broadcasting station, and this level can reach the reference level for general public exposure recommended by the International Commission on Non-Ionizing Radiation Protection (ICNIRP, 1998). This is caused by the fundamental properties of EM fields, namely, reflection and additivity. However, Toropainen (2003) applied radio engineering principles to estimate the power density and SAR levels versus the number of mobile phones in screened environments occupied by humans. The author concluded that it is unlikely that exposure

levels are exceeding the safe limits recommended by the ICNIRP due to multiple mobile phones users in train, elevators, cars, or similar environments.

### **Magnetic Resonance Systems**

Magnetic resonance (MR) systems are used in diagnostic medicine and display images in a format similar to computed tomography. Many safety issues regarding these systems, however, remain as possible concerns. A number of computational reports have predicted the possibility of high SAR levels at high frequencies and formation of hot spots inside the human body at higher field strengths (Collins & Smith, 2001; Kangarlu et al., 2003).

## **BIOLOGICAL EFFECTS**

### **Ornithine Decarboxylase**

Ornithine decarboxylase (ODC) is an important enzyme involved in the regulation of cell growth. Stagg et al. (2001) exposed immobilized Fischer 344 rats in a dose-dependent manner to pulse-modulated (11 packets/s) digital RF fields at 1.6 GHz in accordance with the protocol of the Iridium mobile satellite phone system. When RF-exposed and sham-exposed (immobilized) animals were compared, no differences were seen in core body temperature or corticosterone or adrenocorticotropic hormone (ACTH) levels that could be attributed to near-field RF exposure. ODC activity and fos and jun mRNA levels were also monitored in brains of animals exposed to the RF field for 2 h, and showed no marked differences from sham-exposed (loose-tube immobilized) animals that were exposed to RF fields. Stagg et al. (2001) concluded that the pulse-modulated Iridium signal at SARs up to 5 W/kg is incapable of altering the stress-related responses.

Paulraj and Behari (2002) described the effects of low-level continuous-wave (CW) microwaves (2.45 GHz) on developing 35-d-old Wistar rat brain. The animals were exposed 2 h/d for 35 d at a power density of 0.34 mW/cm<sup>2</sup> (SAR = 0.1 W/kg) in a specially made anechoic chamber. A significant increase in calcium ion efflux and ODC activity was observed in the exposed group compared to control. Correspondingly, a significant decrease in the calcium-dependent protein kinase activity was observed. The results indicated that this type of radiation affects the membrane bound enzymes, which are associated with cell proliferation and differentiation, thereby pointing out a possible role for radiation as a tumor promoter.

### **Intracellular Calcium**

In a study designed to test whether exposure to simulated global system for mobile communication (GSM) phone signals influences the concentration of calcium or calcium signalling patterns in single cells, Cranfield et al. (2001) estimated the intracellular calcium concentration ( $[Ca^{2+}]_i$ ) in the human lymphocyte cell line Jurkat exposed to 915 MHz at 2 W/kg RF fields. The results indicated that there is no clear indication that RF emissions from mobile phones are associated with any changes in intracellular calcium levels or calcium signaling in lymphocytes, although an alteration in the frequency of calcium oscillations was noted in activated cells exposed to pulsed wave RF. On the other hand, Guisasola et al. (2002) showed that 64-MHz RF field exposure, associated with turbo spin echo MR imaging resulted in a significant increase in  $[Ca^{2+}]_i$  in human embryonic lung cells, L-132. However, exposure to MR-related static and gradient fields showed no marked effect on  $[Ca^{2+}]_i$ .

In addition to studies investigating the effects of exposure from RF fields there have been a number of reports evaluating the effect on intracellular calcium levels and cell calcium signaling when exposure is to extremely low-frequency (ELF) magnetic fields. These studies are summarized here because there have been suggestions that it is the ELF modulation of the RF fields that may be responsible for nonthermal biological effects.

Experiments assessed whether long-term exposure to 50-Hz pulsed EM field with a peak magnetic field of 3 millitesla (mT) alters the dynamics of intracellular calcium levels in human astrocytoma cells. Pessina et al. (2001) found that a 50-Hz square-wave exposure of astrocytoma cells

resulted in either a decrease or increase in calcium signaling, depending on the stimulus used. Caffeine-stimulated and unstimulated cells showed an increase while substance P and substance P + caffeine produced a decrease in  $Ca^{2+}$  response. This study suggests that magnetic fields act either on intracellular  $Ca^{2+}$  stores or on the plasma membrane. Moreover, EM fields that affected intracellular calcium levels did not produce cell proliferation or cell death.

Ikehara et al. (2002) investigated possible mechanisms for the effects of a 1.51-T pulsed field associated with a transcranial magnetic stimulator on cultured bovine adrenal chromaffin cells. Previously, this group observed a suppression of  $[Ca^{2+}]_i$  signaling pathway when cells were in a  $Ca^{2+}$ -free medium (Ikehara et al., 1998). This study (Ikehara et al., 2002) revealed that magnetic field exposure inhibits  $Ca^{2+}$  release from intracellular  $Ca^{2+}$  stores, but the  $Ca^{2+}$  flux across the plasma membrane did not change.

Spadaro and Bergstrom (2002) showed an increase in  $Ca^{2+}$  uptake in the rat calvarial bone after 2-h exposure to a pulse 1-m T magnetic field (5 ms burst, 20-burst train, at 15 Hz). These effects were observed immediately after exposure and 24 h later, but not after 48 h.

Obo et al. (2002) found that calcium ion flux across the plasma membrane of PC-12D cells from rat pheochromocytoma did not change when parametric magnetic field exposure conditions were used (static fields <0.07 mT, frequencies 14 to 50 Hz with amplitudes 0.015 to 0.15 mT). Madec et al. (2003) used mouse islets of Langerhans, in which regular oscillations of calcium concentrations can be observed. These oscillations are sustained by processes that imply energetic and inter-intracellular communication. Various magnetic fields were applied (50 Hz or multiples of the natural oscillation frequency) at 0.1 or 1 mT or static at 1 mT. Islets were also exposed to "cyclotron resonance" conditions. There was neither alteration of the fundamental oscillation frequency nor alteration of the degree of organization under all exposure conditions. The authors could not show evidence of alterations of calcium processes under exposure to various magnetic fields.

McCreary et al. (2002) carried out an extensive set of experiments exposing a human transformed lymphocyte cell line (Jurkat) to static 78- $\mu$ T, oscillating (60 Hz, 100  $\mu$ T peak sinusoidal), and the parallel combination of static and oscillating EM fields. This combination has been proposed to couple to a metal ion in a protein well (Lednev, 1991; Blanchard & Blackman et al., 1994). McCreary et al. (2002) indicate that the effect on intracellular calcium is probably small and the sensitivity of cells to magnetic fields may be dependent on the cell cycle. Using similar combined fields, Bauréus Koch et al. (2003) studied calcium efflux in highly purified spinach plasma membrane vesicles. Static magnetic fields ranging from 27 to 37  $\mu$ T, time-varying magnetic fields with frequencies between 7 and 72 Hz, and peak amplitudes between 13 and 114  $\mu$ T were used. They showed that such fields affect the  $Ca^{2+}$  channel protein in cell membranes, and results were in agreement with the theoretical model proposed by Blanchard and Blackman (1994).

Yamaguchi et al. (2002) found that Mc 3T3-E1 pre-osteoblast cells and ROS 17/2.8 differentiated osteoblast cells  $[Ca^{2+}]_i$  were not altered when exposed to 0- to 1.25-mT, 60-Hz sinusoidal magnetic fields. This is despite observed decreases in intercellular communication through gap junctions. Decreased gap junction intercellular communication in synovial fibroblasts exposed to 60-Hz electric fields was reported recently by Marino et al. (2003a). In this study, a significant increase in  $Ca^{2+}$  influx was observed and it was suggested that the alteration in gap junction communication was dependent on  $Ca^{2+}$  influx rather than on changes in membrane potential.

Craviso et al. (2002) studied  $[Ca^{2+}]_i$  in isolated bovine adrenal chromaffin cells exposed to 60-Hz magnetic fields at 0.01, 0.1, 1, 1.4, and 2 mT. With respect to number of cells exhibiting number and types of transients, no significant effects were seen. However, the percentage of cells that responded to a nicotinic cholinergic receptor agonist was significantly higher after 1 d of exposure compared to sham or unexposed cultures. This provides evidence that plasma membrane nicotinic receptors may be affected by the exposure.

In addition to magnetic field effects on  $[Ca^{2+}]_i$ , other reported effects of ELF exposure have been shown to depend on calcium. For example, Zhou et al. (2002) examined the DNA-binding behavior of the transcription factor cyclic-AMP-responsive element binding protein (CREB) in HL60 cells after exposure to a 0.1-mT, 50-Hz ELF sinusoidal magnetic field by a gel shift assay. Magnetic fields induced a time-dependent activation of CREB binding. The complex formation increased

shortly after exposure for 10 min, reaching a peak level after 1 h, and then recovered to basal level at 4 h after exposure. A novel magnetic field-induced activating transcription factor 2 (ATF2/ATF2) homodimer formation was observed after exposure for 30 min, 1 h, and 2 h. The results indicate that magnetic field exposure activates CREB DNA binding through calcium-related signal transduction pathways under these experimental conditions.

Tonini et al. (2001) found that the effects of 50-Hz magnetic field (120 and 240  $\mu$ T) exposure on chemically induced differentiation of neuroblastoma/glioma culture cells, NG108-15, was dependent on the extracellular calcium concentration.

### Cell Proliferation

D'Ambrosio et al. (2002) exposed human peripheral blood cultures to 1.748 GHz, either CW, or phase-only modulated wave (Gaussian minimum shift keying, GMSK). SAR used (5 W/kg) was higher than that occurring in the head of mobile phone users. No marked changes were found in cell proliferation kinetics after exposure to either CW or GMSK fields.

Aldinucci et al. (2003) investigated whether static EM fields at a flux density of 4.75 T, generated by a nuclear magnetic resonance (NMR) apparatus, could promote movements of  $\text{Ca}^{2+}$ , cell proliferation, and the eventual production of proinflammatory cytokines in human peripheral blood mononuclear cells (PBMC) as well as in Jurkat cells, after exposure to the field for 1 h. The same study was also performed after activation of cells with 5 mg/ml phytohemagglutinin (PHA). The results clearly demonstrate that static NMR 4.75-T exposure has neither proliferative, nor activating, nor proinflammatory effects on both normal and PHA-activated PBMC. Exposure of Jurkat cells to static waves significantly decreased the proliferation. Moreover, the concentration of interleukin-1, interleukin-2, interleukin-6, interferon, and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) remained unchanged in exposed cells.

### Blood–Brain Barrier (BBB)

RF-induced breakdown of the blood–brain barrier (BBB) has been studied either alone or in combination with magnetic fields. Leszczynski et al. (2002) reported that heat-shock protein 27 (hsp 27) was transiently increased by nonthermal exposure to a 900-MHz GSM mobile phone signal. Based on the known functions of hsp 27, it was proposed that this might produce an increase in BBB permeability through stabilization of endothelial cell stress fibers. Other studies have not found RF-induced disruption of the BBB (Finnie et al., 2001, 2002). Most of the studies conclude that high-intensity RF fields are required to alter the permeability of the BBB. Salford et al. (2003) demonstrated that extremely low doses of GSM radiation can produce brain damage in rats. The authors reported nerve damage following a single 2-h exposure at a SAR of 2 mW/kg. Data showed that RF energy impaired the BBB, but suggested that the chemicals that leak through the BBB probably damage neurons in the cortex, the hippocampus, and the basal ganglia of the brain.

D'Andrea et al. (2003a) reviewed this subject and concluded:

Effects of RF exposure on the BBB have been generally accepted for exposures that are thermalizing. Low level exposures that report alterations of the BBB remain controversial. Exposure to high levels of RF energy can damage the structure and function of the nervous system. Much research has focused on the neurochemistry of the brain and the reported effects of RF exposure. Research with isolated brain tissue has provided new results that do not seem to rely on thermal mechanisms. (p. S107)

### Melatonin Levels

It has been suggested that RF fields may have a cancer-promoting effect by altering circadian rhythms of pineal activity and melatonin release. The RF field effect on melatonin levels has been explored in several human and animal studies, as presented next.

*Human studies* Griefhan et al. (2001) exposed young healthy male volunteers (16–22 yr) to ELF fields (16.7 Hz). The exposure did not reveal any alteration in salivary melatonin production. The authors concluded that the results of their study lead to the hypothesis that melatonin production suppression in humans most likely occurs only after repeated exposure to intermittent fields.

Radon et al. (2001) conducted a study to evaluate the effects of RF fields used in GSM systems on salivary melatonin, neopterin, and immunoglobulin A (sIgA) levels during and after several hours of exposure. Eight healthy student were exposed to 900 MHz pulsed with 217 Hz (average power flux density of 1 W/m<sup>2</sup>). The results obtained showed that the salivary concentrations of melatonin, cortisol, neopterin, and sIgA did not differ significantly between exposure and sham exposure. Melatonin levels appeared to differ depending on whether exposure was during the day or at night.

Burch et al. (2002) conducted a study of male electric utility workers. Personal 60-Hz magnetic field (MF) and ambient light exposures were characterized on the same days using EMDEX II meters. A repeated-measures analysis was used to assess the effects of cellular telephone use, alone and combined with MF exposures, after adjustment for age, participation month, and light exposure. The authors reported that cellular phone use of greater than 25 min/d was associated with a drop in melatonin levels. This effect, however, was seen only on d 3 of the study. Data indicated that prolonged use of cellular phones may lead to reduced melatonin production, and elevated 60-Hz MF exposures may potentiate this effect. In another small study of 9 healthy males aged 19–29 yr, Bortkiewicz et al. (2002) found no change in melatonin excretion due to exposure from a cellular phone of 1 h (900 MHz, pulsed with 217 Hz, SAR = 1.23 W/kg).

*Animal studies* Tripp et al. (2003) administered circularly polarized 50-Hz magnetic fields to isolated pineals in highly controlled conditions. Melatonin release from isolated Wistar rat pineal glands, dissected 2 h after light onset, ZT 2, was measured in a flow through culture system, during and after exposure to a 4-h magnetic field similar in nature and magnitude to that produced in extremely close proximity to a high-voltage power line (500  $\mu$ T, 50 Hz circularly polarized). No significant alterations in pineal melatonin release were produced by exposure to the magnetic field when compared to sham exposure at <1  $\mu$ T.

Bakos et al. (2003) exposed 72 adult male Wistar rats in 6 independent experiments, 3 of which were done with 900 MHz (100  $\mu$ W/cm<sup>2</sup>) and the other 3 with 1800 MHz (20  $\mu$ W/cm<sup>2</sup>) GSM RF radiation modulated with 218 Hz. The exposures were performed in a gigahertz transverse EM mode (GTEM) cell. The animals were exposed for 2 h between 8:00 a.m. and noon daily during a 14-d exposure period. This exposure was outside the period of responsiveness of the pineal gland. The urine of rats was collected from 12:00 a.m. to 8:00 a.m., collecting from exposed and control animal groups on alternate days. Urinary 6-sulfatoxymelatonin (6SM) concentration was measured by <sup>125</sup>I radioimmunoassay. No change in the 6SM excretion levels of exposed rats ( $n = 18$ ) compared to control group ( $n = 18$ ) was found at either 900 or 1800 MHz.

In a review of the effects of RF radiation on the endocrine system, Black and Heynick (2003) concluded that "There is limited evidence that indicates no interaction between RF radiation and the pineal gland" (p. S187).

### Immune System

Radon et al. (2001) found that mobile phone RF radiation had no marked effect on immune function in eight healthy young men. The men were exposed to 900-MHz fields, pulsed with 217 Hz, pulse width 577  $\mu$ s. An antenna was positioned 10 cm behind the subject's head. The power-flux density was approximately 1 W/m<sup>2</sup>, and the maximum local SAR in the head (averaged over 10 g tissue) was 0.025 W/kg. The study was designed to assess the effects of the RF fields on salivary levels of melatonin, cortisol, neopterin, and immunoglobulin A (IgA). Neopterin and IgA are components of the immune system.

Gatta et al. (2003) found that 900-MHz GSM-modulated radiation for 1, 2, or 4 wk (2 h/d) in a transmission electron microscopy (TEM) cell to a SAR of 1 or 2 W/kg had no significant effects on immune function in mice. Black and Heynick (2003) reviewed the subject and concluded: "Lifetime studies of RF radiation exposed animals show no cumulative adverse effects in their endocrine, hematological, or immune systems" (p. 600).

### Cardiovascular Diseases

Braune et al. (1998) reported that exposure of human volunteers to RF fields of mobile phones (GSM 900 MHz, 2 W, 217 Hz frame repetition rate) increased the sympathetic efferent activity with

elevation in the resting blood pressure by between 5 and 10 mm Hg. However, Braune et al. (2002) repeated their study and summarized that RF fields had no effect on the outcomes. They claimed that their 1998 finding of increased blood pressure in mobile phone users was due to an artifact in the design of the original study.

Black and Heynick (2003) reviewed the subject and concluded: "Cardiovascular tissue is not directly affected adversely in the absence of significant radiofrequency electromagnetic fields (RFEMF) heating or electric currents. The regulation of blood pressure is not influenced by ultra high frequency (UHF) RFEMF at levels commonly encountered in the use of mobile communication devices" (p. 187).

## ADVERSE EFFECTS

### Genotoxicity

A number of laboratory experiments have been conducted to assess possible genotoxic effects of a broad range of different RF frequencies (Table 1). Many of the experiments found no evidence for any direct genotoxic or mutagenic effects of RF fields at different power densities. These include DNA damage (Li et al., 2001; McNamee et al., 2002a, 2002b), damage to chromosomes (Vijayalaxmi et al., 2001a, 2001b; Gadhia et al., 2003), induction of sister chromatid exchange (SCE) (Maes et al., 2001; Gadhia et al., 2003), induction of micronuclei (Vijayalaxmi et al., 2001a, 2001b; Bisht et al., 2002; McNamee et al., 2002a, 2002b; Zeni et al., 2003; Koyama et al., 2003), cell transformation (Roti Roti et al., 2001), and mutation in Big Blue mouse neural tissue (Takahashi et al., 2002).

However, as a part of a comprehensive investigation of the potential genotoxicity of RF signals emitted by several types of mobile phones, Tice et al. (2002) demonstrated that, under protracted exposure, RF fields from mobile phones at an average SAR of at least 5 W/kg can produce strand breaks or other damage to DNA, as well as chromosomal damage in human lymphocytes. The signals studied included voice-modulated 837 MHz generated by an analog signal generator or a time division multiple access (TDMA) mobile phone, unmodulated 837 MHz from a code division multiple access (CDMA) mobile phone, and voice-modulated 1909.8 MHz from a personal communication system (PCS) mobile phone via a GSM system.

Similar findings were reported by D'Ambrosio et al. (2002) while irradiating diluted blood with 1748 MHz either as a CW or a GMSK signal for 15 min at 5 W/kg. This study was conducted without the concurrent TDMA amplitude modulation used in GSM 1800 mobile phones. Mashevich et al. (2003) also reported genotoxic effects when radiating human lymphocytes to continuous 830 MHz RF energy at SAR in the range 1.6–8.8 W/kg for 72 h.

Sykes et al. (2001) exposed a group of pKZI mice to pulsed 900-MHz RF radiation (4 W/kg) daily for 30 min. The exposure employed a plane-wave field with a pulse repetition frequency of 217 Hz and a pulse width of 0.6 ms for 1, 5, or 25 d. Three days after the last exposure, spleen sections were screened for DNA inversion events. No significant differences were observed between the control and the exposed groups in the 1- and 5-d exposure groups. In a 25-d exposure group, the authors observed a significant reduction in the inversions below the spontaneous frequency. The observation suggest that exposure to RF field can lead to a perturbation in the recombination frequency, which may have implications for recombination repair of DNA.

Zhang et al. (2002) exposed human blood cells to 2450-MHz RF radiation for 2 h at 5 mW/cm<sup>2</sup> and/or a chemical carcinogen. The RF radiation alone was not genotoxic (DNA strand breaks and micronucleus assay), but was reported to enhance the genotoxic effects of the chemical carcinogen. There is insufficient information about the RF exposure conditions to exclude heat-induced effects.

Meltz (2003) reviewed the *in vitro* literature relevant to the issue of the possible induction of toxicity, genotoxicity, and transformation of mammalian cells due to RF exposure. According to the author, the review was conducted from the perspective of technical merit and also biological consistency, especially with regard to those publications reporting a positive effect. Meltz concludes:

**TABLE 1.** Summary of RF Studies on Cancer-Related Endpoints

| Reference                                     | Type of study   | Exposure  | Results  |
|---|---|---|--|
| <b>DNA damage</b>                             |   |   |  |
| Li et al., 2001                               | Mammalian cultured C3H 10T(1/2) cells.                                  | 847.74 MHz CDMA and 835.62 FDMA; 3.2–5.1 W/kg; 37°C; 2, 4, or 24 h.   | Exposure did not induce measurable DNA damage.   |
| McNamee et al., 2002a, 2002b                  | Blood cultures from human volunteers.                                   | 1.9 GHz pulse-modulated RF; 0–10 W/kg; 37.0 ± 0.5°C; 2 h.   | No DNA damage in cultured human leukocytes.  |
| Sykes et al., 2001                            | PKZ1 mice.  | 900 MHz; 4 W/kg pulsed; with a pulse repetition frequency of 217 Hz and a pulse width of 0.6 ms; 30 min for 1, 5, or 25 d.        | RF radiation can lead to a perturbation in recombination frequency which may have implications for recombination repair of DNA.  |
| Zhang et al., 2002                            | Human lymphocytes.  | Mitomycin C and 2450 MHz; 5.0 mWc/m <sup>2</sup> ; 2 h or only exposed to MMC (0.0125 mg/ml, 0.025 mg/ml and 0.1 mg/ml) for 24 h. | The radiation cannot induce DNA and chromosome damage, but can increase DNA damage effect induced by MMC in comet assay.   |
| <b>Damage to chromosomes</b>                  |   |   |  |
| Vijayalaxmi et al., 2001a, 2001b              | Peripheral blood samples from four healthy nonsmoking human volunteers. | 847.74 MHz CW CDMA; 95 mW/cm <sup>2</sup> (4.9 or 5.5 W/kg); 37 ± 0.3°C.  | No incidence for induction of chromosome aberrations and micronuclei in human blood lymphocytes.   |
| Gadhia et al., 2003                           | Blood samples of 12 mobile phone users.                                 | 935–960 MHz GMSK.   | There was a significant increase in dicentric chromosomes among mobile users who were smoker-alcoholic as compared to nonsmoker-nonalcoholic.  |
| Tice et al., 2002                             | In vitro human blood leukocytes and lymphocytes.                        | 837 MHz TDMA/CDMA and 1909.8 MHz GSM; 1.0–10.0 W/kg; 37 ± 1°C; 3 or 24 h.   | Under extended exposure conditions, RF signals at an average SAR of at least 5 W/kg are capable of inducing chromosomal damage in human lymphocytes.   |
| Mashevich et al., 2003                        | In vitro exposure of human peripheral blood lymphocytes.                | 830 MHz CW; 1.6–8.8 W/kg; 34.5–37.5°C; 72 h.  | Genotoxic effect of EM radiation is elicited via a non-thermal pathway.  |
| <b>Induction of sister chromatid exchange</b> |   |   |  |
| Maes et al., 2001                             | Human lymphocytes.  | 900 MHz alone and combined to the chemical or physical mutagens mitomycin C and X-rays 0 and 10 W/kg.                             | No indication was found of a mutagenic, and/or comutagenic/synergistic effect.   |
| <b>Induction of micronuclei</b>               |   |   |  |
| Vijayalaxmi et al., 2001a, 2001b              | In vitro human blood lymphocytes.                                       | 847.74 MHz CDMA; 4.9 or 5.5 W/kg; 37 ± 1°C for 48 or 72 h.  | There was no evidence for induction of chromosome aberrations and micronuclei.   |
| Bisht et al., 2002                            | C3H 10T* cells.   | 835.62 FDMA (3.2 or 4.8 W/kg) or 847.74 MHz CDMA (3.2 or 5.1 W/kg); 3, 8, 16, or 24 h   | RF radiations does not induce micronuclei.   |
| Zeni et al., 2003                             | Human peripheral blood lymphocytes from 20 healthy donors               | 900 MHz GSM; 0.2 W/kg; 1 h per day for 3 d. 1.6 W/kg for 6 min followed by a 3-h pause.   | No statistically significant differences were detected in any case in terms of either micronucleus frequency or cell cycle kinetics.   |
| Koyama et al., 2003                           | Chinese hamster ovary (CHO)-K1 cells.                                   | 2.45 GHz; 5, 10, 20, 50, 100, and 200 W/kg; 37, 38, 39, 40, 41, and 42°C; 2 h.  | The micronucleus frequency in cells exposed to radiation at a SAR of lower than 50 W/kg did not differ from the sham-exposed controls, while those at SARs of 100 and 200 W/kg were significantly higher when compared with the sham-exposed controls. An increase in SAR causes a rise in temperature which may be connected to the increase in micronucleus formation generated by exposure to RF. |

(Continued)

**TABLE 1.** (Continued)

| Reference                                 | Type of study                   | Exposure  | Results   |
|---|---------------------------------|---|---|
| D'Ambrosio et al., 2002                   | In vitro human lymphocytes      | 1.748 GHz CW or GMSK; 5 W/kg; 15 min.                       | The micronucleus frequency result was not affected by CW exposure; however, a statistically significant micronucleus effect was found following exposure to phase modulated field. The results suggest a genotoxic power of the phase modulation. |
| <b>Mutation</b><br>Takahashi et al., 2002 | Brain tissues of Big Blue mice. | 1.5 GHz; 2.0, 0.67, and 0 W/kg; 90 min/d, 5 d/wk. for 4 wk. | Radiation is not mutagenic to mouse brain cells and does not create any increased hazard with regard to brain tumor development.  |

The weight of evidence available indicates that, for a variety of frequencies and modulations with both short and long exposure times, at exposure levels that do not (or in some instances do) heat the biological sample such that there is a measurable increase in temperature, RF exposure does not induce (a) DNA strand breaks, (b) chromosome aberrations, (c) sister chromatid exchanges (SCEs), (d) DNA repair synthesis, (e) phenotypic mutation, or (f) transformation (cancer-like changes). (p. 196)

### Carcinogenicity

As RF exposure is not considered to be directly carcinogenic, research is aimed toward its possible promotional and co-promotional effects. Table 2 summarizes major RF studies on carcinogenicity. Three studies have suggested that high levels of exposure to RF fields may be associated with an increased tumor incidence in animals (Repacholi et al., 1997; Trosic et al., 2002; Zhang et al., 2002). However, Utteridge et al. (2002) could not replicate the increase in lymphoma either in normal mice or in the same lymphoma-prone mice reported by Repacholi et al. (1997). The work of Utteridge et al. (2002) has been criticized because of a number of unresolved issues concerning design and analysis of these studies (Kundi, 2003; Goldstein et al., 2003; Lerchl, 2003).

Other studies have shown no change in tumor development rates (Zook & Simmens, 2001; Mason et al. 2001; Jauchem et al., 2001; Heikkinen et al., 2001, 2003; Imaida et al. 2001; Bartsch et al., 2002; Anane et al., 2003; La Regina et al., 2003) at moderate levels of exposure to RF fields.

Repeated exposure to mobile phone radiation was found to act as a repetitive stress leading to continuous expression of heat-shock proteins (Hsps) in exposed cells and tissues, which in turn affects their normal regulation. This hypothesis, which was presented by French et al. (2001), provides the possibility of a direct association between mobile phone use and cancer. The authors cite evidence that Hsps can play a role in cancer induction or promotion, though they state that there is debate as to whether the association with cancer is causal or correlative. They suggest that recurrent exposure to frequent mobile phone use could lead to chronic expression of Hsps in the brain tissue of users and that this in turn might induce or promote cancer.

Di Carlo et al. (2002) exposed chicken embryos to ELF-EM fields (8  $\mu$ T) continuously for 4 d, or to ELF or RF exposures (3.5 mW incident power) repeated daily for 4 d. Several of the exposure protocols yielded embryos that had statistically significant decrease in protection against hypoxic stress. Following 4 d of ELF-EM exposure, Hsp 70 levels declined by 27% as compared to controls. The superposition of ELF-EMF noise, previously shown to minimize ELF-EMF-induced hypoxia protection (Di Carlo et al., 1999), inhibited hypoxia deprotection caused by long-term, continuous ELF or daily, repeated RF exposures. The authors concluded that this EM-induced decrease in Hsp 70 levels and resulting decline in cytoprotection suggest a mechanism by which daily exposure could enhance the risk of cancer and other adverse health outcomes.

Shallom et al. (2002) exposed chick embryos to 915 MHz radiation at approximate SARs of 1.5 and 2.5 W/kg in different experiments. Levels of Hsp 70 were found to increase by approximately

**TABLE 2.** Summary of RF Studies on Carcinogenicity

| Reference                  | Type of study   | Exposure   | Results   |
|----------------------------|---|--|---|
| <b>Tumor development</b>   |   |  |   |
| Trošić et al., 2002        | Adult male Wistar.  | 2450 MHz; 5–10 mW/cm <sup>2</sup> ; 2 h a day, 7 d/wk for up to 30 d.  | Proliferation and maturation of nucleated erythropoietic cells were affected.   |
| Utteridge et al., 2002     | 120 E mu-Pim 1 heterozygous mice and 120 wild-type mice.                                    | 898.4 MHz GSM; 1 h/d, 5 d/wk for up to 104 wk.   | There was no significant difference in the incidence of lymphomas.  |
| Zook and Simmens, 2001     | Sprague-Dawley rats from 2 to 24 m of age.  | 860 MHz CW and pulsed; 1.0 W/kg; 6 h/d, 5 d/wk.  | No statistically significant effect on the number, volume, location, multiplicity, histological type, malignancy or fatality of brain tumors.   |
| Mason et al., 2001         | SENCAR mouse model of skin.   | 94 GHz; (1.0 W/cm <sup>2</sup> for 10 s) or repeated (2 exposures/wk for 12 wk, 333 mW/cm <sup>2</sup> for 10 s).                                  | Exposure does not promote or copromote papilloma development in this animal model of skin carcinogenesis.   |
| Jauchem et al., 2001       | C3H/HeJ mice  | Ultra-wideband (rise time 176 ps, fall time 3.5 ns, pulse width 1.9 ns, peak E-field 40 kV/m, repetition rate 1 kHz); 2 min once a week for 12 wk. | Lack of effects of UWB-pulse exposure on promotion of mammary tumors in a well-established animal model of mammary cancer.  |
| Heikkinen et al., 2001     | Two hundred female CBA/S mice.  | 902.5 MHz NMT (1.5 W/kg) and GSM (0.35 W/kg); 1.5 h per day, 5 d/wk for 78 wk.   | The RF radiation exposures did not increase the incidence of any neoplastic lesion significantly.   |
| Imaida et al., 2001        | Ten-week-old ICR female mice.   | 1.5 GHz initiated by 7.12-dimethylbenz[a]anthracene (DMBA); peak SAR 2.0 W/kg, whole body average SAR 0.084 W/kg; 90 min/d 5 d/wk, for 19 wk.      | No effect on skin tumorigenesis.  |
| Bartsch et al., 2002       | 7,12-Dimethylbenz[a]anthracene (DMBA)-induced mammary tumors in female Sprague-Dawley rats. | GSM-like signal at 900 MHz; 100 μW/cm <sup>2</sup> ± 3 dB; 17.5–70 mW/kg.  | There was no statistically significant effect of RF exposure on tumor latency. The cumulative tumor incidence at the end of the experiment was unaffected as well.  |
| Anane et al., 2003         | Mammary-gland tumors in female Sprague-Dawley rats.   | 900 MHz GSM; 3.5, 2.2, and 1.4 W/kg in the first experiment and 1.4, 0.7 and 0.1 W/kg in the second experiment; 2 h/d, 5 d/wk for 9 wk.            | No evidence of a copromoting effect.  |
| La Regina et al., 2003     | F344 rats.  | 835.62 MHz FDMA; 847.74 MHz CDMA; 0.85 ± 0.34 W/kg; 4 h per day, 5 d/wk over 2 yr.   | No significant effect on the incidence of spontaneous tumors.   |
| <b>Heat-shock proteins</b> |   |  |   |
| Di Carlo et al., 2002      | Chick embryos.  | ELF-EMFs (8 T) continuously for 4 d or to ELF/RF at 3.5 mW; daily (20, 30, or 60 min once or twice daily for 4 d).                                 | Following 4 d of exposure, HSP70 levels decline by 27% as compared to controls.   |
| Shallom et al., 2002       | Chick embryos.  | Athermal 915 MHz.  | Levels of Hsp70 were found to increase within 2 h. Not only can athermal microwave exposures activate the stress protein response pathway: they can also enhance survivability following exposure to a subsequent, potentially lethal stress. |

30% compared to controls, with peak expression occurring by 3 h from the start of exposure. Final temperatures, measured with thermocouples situated next to the embryos, did not exceed 38.8°C. The authors did not feel that this temperature was responsible for the increased production of Hsp 70, since heating of the chick embryos to 39°C did not produce an increase in Hsp 70 levels. The

authors concluded that their study provides support for the hypothesis that "athermal EM field exposures induce Hsp 70 expression." This finding is supported by another study (Kwee et al., 2001). Moreover, De Pomerai et al. (2003) emphasized that RF radiation enhances the aggregation of bovine serum albumin in vitro in a time- and temperature-dependent manner. RF radiation also promotes amyloid fibril formation by bovine insulin at 60°C. These alterations in protein conformation are not accompanied by measurable temperature changes, consistent with estimates from field modeling of the SAR (15–20 mW/kg). Limited denaturation of cellular proteins could explain a previous observation (De Pomerai et al., 2000) that modest heat-shock responses are induced by RF exposure in *Caenorhabditis elegans*. The authors also show that heat-shock responses both to heat and RF are suppressed after RNA interference ablating heat-shock factor function.

Heynick et al. (2003) reviewed studies on cancer and related effects from exposure to EM fields in the nominal frequency range of 3 kHz to 300 GHz. They concluded: "The preponderance of published epidemiologic and experimental findings do not support the supposition that *in vivo* or *in vitro* exposures to such fields are carcinogenic" (p. S74).

### Testicular Function and Teratogenicity

Table 3 summarizes RF studies on testicular function and teratogenicity. Bol'shakov et al. (2002) studied the combined effect of 460-MHz RF radiation and increased (up to 40°C) temperature on *Drosophila* embryos. It was demonstrated that the effect of 5-min exposures to nonmodulated microwaves with 6 W/kg SAR accompanied by heating is only a little stronger than at normal temperature (24.5°C). Irradiation with pulse-modulated microwaves at pulse repetition rates of 6, 10, 16, and 22 pps (pulses per second) with average SAR of 0.12 W/kg (pulsed SAR 3 W/kg) combined with increased temperature caused some changes in pelvic inflammatory disease (PID) dependent on the pulse rate. At 6 and 22 pps, the increase in PID was close to that observed at normal temperature, while at 10 and 16 pps the microwave irradiation did not produce any noticeable effect on development of the *Drosophila* embryos. The results of the study indicated that RF radiation did not produce any effect on development of *Drosophila*.

Elbetieha et al. (2002) exposed male and female mice to 50-Hz magnetic fields at 25 mT for 90 d before the mice were mated with unexposed counterparts. There were no significant effects on the weights of the testes, seminal vesicles, preputial gland, or body weights of males exposed to 50-Hz magnetic field. Body and uterine weights were not affected in females, but ovarian weight was significantly increased. It was concluded that exposure of male and female mice to a low-frequency magnetic field had no adverse effects on fertility and reproduction in mice.

**TABLE 3.** Summary of RF Studies on Testicular Function and Teratogenicity

| Reference               | Type of study                    | Exposure   | Results   |
|-------------------------|----------------------------------|--|---|
| Bol'shakov et al., 2002 | <i>Drosophila</i> embryos        | 460 MHz at average SAR 0.12 W/kg (pulsed SAR 3 W/kg) and increased temperature up to 40°C. Pulse repetition rates of 6, 10, 16, 22 pps.  | No effect on the development of the <i>Drosophila</i> embryos at 10 and 16 pps. Increase in PID at 6 and 22 pps (close to the observation at normal temperature). |
| Elbetieha et al., 2002  | Adult male and female Swiss mice | ELF 50 Hz sinusoidal magnetic field, 25 µT (rms); 90 d.  | No adverse effects on fertility and reproduction in mice.   |
| Ohnishi et al., 2002    | Male and female ICR mice         | ELF 50 Hz, 0.5 mT and 5.0 mT (rms) for 9 and 2 wk prior to mating for males and females, respectively.   | No major effects on reproduction and development in mice.   |
| Dasdag et al., 2003     | Sprague-Dawley rats              | RFR from cellular phone placed 0.5 cm under the cage, 250 mW radiated power, 0.52 W/kg (whole body average SAR) and 3.13 W/kg (1 g averaged peak SAR): 20 min/d, 7 d/wk for 1 m. | No evidence of adverse effects of mobile phone exposure on measures of testicular function or structure.  |

Ohnishi et al. (2002) found that magnetic fields (50 Hz, 0.5 mT and 5.0 mT, for 2 or 9 wk) have no major effects on reproduction and development in mice, and do not support the association of EM exposure with adverse reproductive effects suggested in the epidemiological literatures.

Dasdag et al. (2003) investigated the effect of RF radiation emitted from cellular phones on the lipid composition, malondialdehyde concentration, p53 immune reactivity, sperm count, morphology, histological structure of testes, and rectal temperature of rats. For 250-mW radiated power, the whole body average SAR was 0.52 W/kg and 1 g averaged peak SAR was 3.13 W/kg. The results indicated that there was no statistically significant alteration in any of the assayed endpoints. Hence, this study found no evidence suggesting an adverse effect of mobile phone exposure on measures of testicular function or structure.

## EPIDEMIOLOGICAL STUDIES

At the time of release of the Royal Society of Canada report in 1999, the epidemiologic research was considered to be inadequate to provide evidence as to whether exposure to mobile phones or RF fields carried an increased risk of cancer or other detrimental health effects. Several epidemiological studies published in 1999 and 2000 were reviewed in an update to that report published in this journal (Krewski et al., 2001a, 2001b). The following review describes the studies published since that time, including several case-control and cohort investigations of mobile phone users, and updates to previous cohort investigations.

### Studies of Mobile Phone Users

Table 4 summarizes epidemiological studies of mobile phone and cancer. Muscat et al. (2000) carried out a case-control study of brain cancer in the northeastern United States, involving 469 cases diagnosed between 1994 and 1998, and 422 hospital-based controls. Self-reported exposure included information on frequency, duration, and laterality of use of cellular phones, and information on potential modifiers. Median monthly extent of use was 2.5 h for cases and 2.2 h for controls. Mean duration of use was 2.8 yr for cases and 2.7 yr for controls. Adjusted risk of brain cancer with regular or ever use of a cellular phone in this study group was 0.85 (95% CI, 0.6–1.2). No relationship of brain cancer risk and duration or frequency of use of a cellular phone was observed in this study when the odds ratio (OR) for infrequent users was 1.0 or when OR for frequent users was 0.7 ( $p$  value for duration of use = .54). Neither was there any relationship of risk with brain cancer subtype, except for neuroepitheliomatous cancer (OR = 2.1; 95% CI, 0.9–4.7), based on 35 cases, 10 of which were located in the temporal lobe. Laterality of phone use was not associated with location of temporal lobe tumors.

Another case-control study of brain tumors was carried out in the United States, involving 782 cases of intracranial tumors of the nervous system identified between 1994 and 1998, and 799 hospital-based controls, by Inskip et al. (2001). Information on type of mobile phone, start and end of time of use, duration of "regular" use, frequency of use, and hand used to hold the phone was ascertained by self-report. Results were adjusted for socioeconomic variables and history of medical exposure to ionizing radiation. No association was observed between ever use or regular use of a cell phone and risk of any of the types of brain tumor (OR = 0.9 overall; 0.6 for high-exposed group); nor was a higher risk identified for those with longer use, increasing duration or frequency, or total cumulative use of cellular phones. No association was seen between laterality of tumor and laterality of phone use.

Both of these studies were unable to assess risks of long-term use and use of the newer digital phones. Because both studies were of case-control design, there is also a potential for bias due to nonrepresentative control selection and incomplete participation rates, and potential for error in self-reports of phone use.

Johansen et al. (2001) has reported on the cancer experience of a cohort of over 420,000 private cellular phone subscribers in Denmark from 1982 to 1995. Overall, 3391 cancers were identified through the Danish Cancer Registry among these subscribers. The cohort had a significantly decreased standardized cancer incidence ratio (SIR) of 0.89, mainly accounted for by decreased

**TABLE 4.** Summary of Epidemiological Studies of Mobile Phones and Cancer Risk

| Reference             | Type of study  | Exposure   | Results   | Comments  |  |
|-----------------------|--|--|---|---|--|
| <b>Brain tumors</b>   |  |  |   |   |  |
| Muscat et al., 2000   | Hospital-based case-control study involving patients in 5 U.S. academic medical centres, 1994–1998, with 469 brain cancer cases and 422 controls.  | Use of hand-held cellular telephones, in hours per month and years of use, obtained from patient interviews.   | OR = 0.85 (0.6–1.2)   | No significant association between primary brain cancer and years of mobile phone use, number of hours of use per month, or the cumulative number of hours of use. There was a tendency ( $p = .06$ ) for laterality in this study. |  |
| 300                   | Inskip et al., 2001  | Hospital-based case-control study involving patients at Phoenix, AZ; Boston; and Pittsburgh hospitals, 1994–1998, with 489 glioma cases, 197 meningioma cases, 96 acoustic neuroma case, and 799 controls. | Self and proxy reported use of hand-held cellular telephones; duration and frequency (in persons reporting $>5$ times of mobile use).                   | OR = 1.0 (0.6–1.5) Glioma: 0.9 (0.5–1.6) Meningioma: 0.2 (0.3–1.7)<br>Acoustic neuroma: 1.4 (0.6–3.5)<br>Odds ratios are for more than 100 h of use.  | The results do not support the existence of an association between mobile phone use and certain cancers (glioma, meningioma, or acoustic neuroma). There was no difference for side of head. |
| Johansen et al., 2001 | Retrospective population-based cohort study involving 420,095 cellular telephone subscribers in Denmark, 1982–1995, with 3391 cancers.   | Use of cellular telephone; computerized files of two Danish operators.   | SIR = 0.89 (0.86–0.92);<br>Brain: SIR = 0.95 (0.81–1.12)<br>Salivary gland: SIR = 0.72 (0.29–1.49)<br>Leukemia: SIR = 0.97 (0.78–1.21)                  | No relationship between brain tumor risk and RF radiation compared by duration of phone use, date since first subscription, age at first subscription, or type of phone used.   |  |
| Auvinen et al., 2002  | Population-based case-control study involving subjects from cancer registry in Finland, 1996, with 398 brain tumor case; 198 glioma cases; and 34 salivary-gland cases. There were 5 controls selected per case. | Use of cellular phones, computerized records from the two cellular network providers in Finland.   | Brain tumor: OR = 1.3 (0.9–1.8)<br>Salivary gland: OR = 1.3 (0.4–4.7)<br>Gliomas: OR = 2.1 (1.3–3.4) (analog)<br>Gliomas: OR = 1.0 (0.5–2.0) (digital). | No clear association between use of mobile phones and risk of cancer has been provided.   |  |
| Muscat et al., 2002   | Hospital-based case-control study involving patients from New York University and New York Presbyterian Medical centers, 1997–1999, with 90 cases of acoustic neuroma and 86 controls.                           | Self reported cellular phone use; frequency, duration, and lifetime hours of use.  | Up to 60 h of use: OR = 0.7 (0.2–0.6)<br>3–6 yr of use: OR = 1.7 (0.5–5.1)  | Although there was an elevated risk with 3 or more years of phone use, these longer-term users were also the most infrequent users, and there was no association with cumulative use.   |  |

|                            |   |   |  |  |
|----------------------------|---|---|--|--|
| Hardell et al., 2002a      | Population-based case-control study involving patients from four medical regions in Sweden, 1997–2000, 1303 brain tumor cases and controls.   | Self-reported use of cellular and cordless telephones; type of telephone (analog or digital), years of use, mean number and length of daily calls and brand name. Cumulative use (h) for all years. | For $>1$ yr latency<br>Analog: OR = 1.3 (1.02–1.6)<br>Digital: OR = 1.0 (0.8–1.2)<br>Cordless: OR = 1.0 (0.8–1.2)          | Significant association for analog and cordless phones and all tumors. No evidence of phones response by duration of phone use.  |
| Hardell et al., 2002b      | Population-based case-control study involving patients from four medical regions in Sweden, 1997–2000, 588 malignant brain tumor cases, and 581 controls.                               | Self-reported use of cellular and cordless telephones; type of telephone (analog or digital), years of use, mean number and length of daily calls and brand name. Cumulative use (h) for all years. | For cordless: OR = 1.5 For analog phone: OR = 3.7  | Statistically significant results for analog and cordless phones. Multivariate analysis not significant. No increased risk with longer duration, except for cordless.  |
| Hardell et al., 2003a      | Population-based case-control study involving patients from four medical regions in Sweden, 1997–2000, 1429 brain tumor case, and 1470 controls.  | Self-reported use of cellular and cordless telephones; type of telephone (analog or digital), years of use, mean number and length of daily calls and brand name. Cumulative use (h) for all years. | For $>1$ yr latency<br>Analog: OR = 3.45 (1.77–6.76)<br>Digital: OR = 1.21 (0.66–2.22)<br>Cordless: OR = 1.03 (0.62–1.72). | Some of the statistically significant results are surprising. For instance OR for cordless phones for astrocytomas of 1.5 is unusual.  |
| Hardell et al., 2003b      | Population based case-control study involving cases from Swedish Cancer Registry, 1960–1979, vestibular schwannoma (VS).  | Self-reported use of cellular and cordless telephones; type of telephone (analog or digital), years of use, mean number and length of daily calls and brand name. Cumulative use (h) for all years. | For $>1$ yr latency<br>Analog: OR = 3.45 (1.77–6.76)<br>Digital: OR = 1.21 (0.66–2.22)<br>Cordless: OR = 1.03 (0.62–1.72). | A significant increased risk for VS was found for analog phone users. Digital and cordless phones also revealed an increased but not significant risk.   |
| Warren et al., 2003        | Hospital-based case-control study involving patients from academic tertiary case medical centre, USA, 1995–2000, with 18 intratemporal facial nerve (IFN) tumor cases and 192 controls. | Self-reported use of cellular telephone; type, duration, or regular use ( $>1$ call/wk).  | OR = 0.6 (0.2–1.9)   | Regular cellular telephone use does not appear to be associated with a higher risk of IFN tumor development. The short duration of widespread cellular telephone use precludes definite exculpation as a risk for IFN tumor development. |
| <b>Melanoma of the eye</b> |   | Self-reported occupational exposure to electromagnetic radiation, sources, production processes, job tasks, etc.  | OR = 3.0 (1.4–6.3).  | Association between RF exposure from mobile phones and uveal melanoma.   |

risk of cancer of the lung and other smoking-related cancers. No increased risk was observed for cancers of the brain or nervous system ( $SIR = 0.95$ ; 95% CI, 0.81–1.12), for salivary gland ( $SIR = 0.72$ ; 95% CI, 0.29–1.49), or for leukemia ( $SIR = 0.97$ ; 95% CI, 0.78–1.21). No effect was seen also by type of phone (analogue or digital), duration of use, or time or age since first subscription. The large study size meant the authors were able to assess many different types and subtypes of cancer with reasonable precision. In addition, being population-based, this study avoided problems associated with incomplete ascertainment or participation of subjects. However, it was not able to adjust for other modifiers of risk, and the study investigators did not have information specifically on the phone user or use of corporate cellular phones.

In a population-based case-control study of 1617 cases of brain tumor identified and still alive in Sweden from January 1997 to June 2000 (Hardell et al., 2002a), a 30% increased risk was observed among users of analogue phones, which rose to 80% for those with greater than 10 yr of use. The increase was confined to those with benign tumors, in particular acoustic neuromas. Laterality of phone use was also identified in this study as affecting risk for analog phone users, for temporal and other areas of the brain. Users of cordless phones and digital cell phones showed no increased risk, but the follow-up time was shorter for these phone types. A separate analysis of 649 patients aged 20–80 yr of both sexes with malignant brain tumor diagnosed from 1 January 1997 to 30 June 2000 (Hardell et al., 2002b) showed no overall increased risk with cell phone use. However, use of either an analog or a digital phone on the same side of the head as the tumor was associated with an increased risk of brain cancer.

Data on acoustic neuromas and benign and malignant brain tumors from the previous studies (Hardell et al., 2002a, 2002b) were reported recently (Hardell et al., 2003a, 2003b) with different analysis. The results show a change in incidence of acoustic neuroma in the Swedish cancer registry between 1980 and 1998.

In Finland, a file of over 500,000 private cellular phone subscribers was linked to the cancer registry (Auvinen et al., 2002), and a case-control study of 398 brain tumor patients and 34 salivary-gland tumor patients was carried out, using 5 controls per case. Information on type of phone (analog or digital) and on start and end date of phone subscription was available. The analysis was adjusted for socioeconomic status, categories of urban status, and occupational groupings. Approximately 13% of the cases of brain tumors, 12% of the cases with salivary gland tumors, and 11% of the controls never had a personal subscription to a cellular phone provider. Average duration of subscription was 2–3 yr for analog phone users, and less than 1 year for digital phone users. The OR for brain tumors with more than 2 yr of phone use was 1.5 (95% CI, 0.9–2.5), based on only 18 cases; the OR for salivary gland tumors with more than 2 yr of phone use was 2.3 (95% CI, 0.2–25.3), based on only 1 case. The authors concluded that cellular phone use was not associated with brain tumors or salivary-gland cancers overall, but there was a weak association between gliomas and analog cellular phones. A register-based approach has limited value in risk assessment of cellular phone use because of the lack of information on the levels of exposure to RF fields.

Two studies also reported on risk of acoustic neuroma with cellular phone use. Inskip et al. (2001) found no significant increase in the risk of acoustic neuroma (OR = 1.4; 95% CI, 0.6–3.5) in their large case-control study of all primary brain tumors. However, this study involved only 96 cases of acoustic neuroma, and only 5 used a mobile phone for 5 yr or more. Muscat et al. (2002) reported the results of a hospital-based case-control study of acoustic neuroma cases, diagnosed from 1997 to 1999 in New York. They observed an adjusted OR of 0.7 (95% CI, 0.2–2.6) for greater than 60 total hours of use of a cellular phone, based on 9 cases. Risk did not vary significantly by frequency and duration of use. Muscat et al. (2002) noted a tendency for an inverse laterality effect that might be attributable to hearing problems at the side of the tumor.

Warren et al. (2003) explored the hypothesis that cellular phone use may induce intratemporal facial nerve (IFN) tumors. Eighteen patients with IFN tumor, diagnosed between 1995 and 2000, were matched with controls. Interviews were conducted and covered details of cellular phone use, medical history, occupational history, and personal habits. Patients with IFN tumors ( $n = 18$ ) were case-matched with patients treated for acoustic neuroma ( $n = 51$ ), rhinosinusitis ( $n = 72$ ), and dysphonia or gastroesophageal reflux disease ( $n = 69$ ). Risk of facial nerve tumorigenesis was compared

by extent of cellular telephone use and other risk factors. There was no association with regular use of hand-held cellular phones in those with IFN tumor ( $OR = 0.4$ ; 95% CI, 0.1–2.1) or in subjects with acoustic neuroma ( $OR = 1.0$ ; 95% CI, 0.4–2.2). The OR of developing an IFN tumor with any hand-held cellular phone use was 0.6 (95% CI, 0.2–1.9). The authors caution that the number of subjects was small and that the period of exposure was short.

Stang et al. (2001) reported on risk of uveal melanoma (melanoma of the eye) with self-reported occupational use of radio sets, mobile phones, or similar devices in a combined analysis of two case-control studies in Germany. A significant fourfold increase in risk was identified, based on 12 exposed cases. The authors speculate that RF radiation might act as a cancer promoter, by inhibiting melatonin production by cells in the retina and ciliary body, which in turn might remove a block to proliferation of potentially cancerous cells. Exposure assessment in this study was insufficient for adequate characterization of exposure. In contrast, no relationship between cellular phone use and uveal melanoma was observed in the Danish cohort study (Johansen et al., 2001), based on eight cases of ocular cancer ( $SIR = 0.59$ ; 95% CI, 0.25–1.17). It should be noted that Stang et al. (2001) investigated only occupational use of mobile phones, while Johansen et al. (2001) excluded occupational use.

### Other Radiofrequency Field Exposures

Cooper et al. (2001) updated the earlier studies by Dolk et al. (1997a, 1997b) of adult and childhood leukemia around the Sutton Mast radio and TV transmitters in the West Midlands area of the United Kingdom. Cancer data from 1987 to 1994 indicated that none of the adults had elevated cancer risk within 2 km of the source, although over the entire study area within 10 km of the source, significant increase in risk of female hematopoietic and lymphatic cancers, specifically acute myeloid, all leukemias, and chronic lymphatic leukemia was seen; an increase was also seen in risk of male acute lymphatic leukemia. The original results of the Dolk study, a decreasing risk with distance for leukemia in adults and some subgroups, were not replicated. There were too few childhood leukemia cases (26 in total) to reach conclusions on childhood leukemia risk. The results of the update of Dolk et al. (1997a) by Cooper et al. (2001) are in line with the previous findings. The original results in close proximity of the tower were based on very few cases. Dolk et al. (1997a) started from the assumption that RF radiation decreases with increasing distance to the tower, whereas the highest exposure is expected at a distance between 1 and 5 km when the main beam reaches ground level.

Michelozzi et al. (2002) investigated the risk of adult and childhood leukemias near the Vatican high-power radio station in Rome, Italy. Forty adult leukemia deaths were reported between 1987 and 1998, within a 10-km radius of the station. The population of this area was 49,656 residents in 1991. Eight childhood leukemia cases were identified in the same area between 1987 and 1999. Although some variation in risk was observed for childhood leukemia with distance up to 6 km from the station ( $SIR = 2.2$ , 95% CI, 1.0–4.1), and there was the suggestion of a decrease in risk with increasing distance for childhood leukemia ( $p = .036$ ) and for male adult leukemia mortality ( $p = .03$ ), small numbers and the lack of individual exposure estimates preclude conclusions based on these results.

### Occupational Exposed Populations

Results of a case-control study of neuroblastoma and parental occupational exposures to EM fields, specifically exposures to electrical equipment and radiation sources, were reported by De Roos et al. (2001). This study updates an earlier analysis based on parental job title (Olshan et al., 1999) of 538 cases from the United States and Canada and controls obtained through random digit dialing. This new analysis uses a job exposure matrix combining self-reported job title and exposures by source, reviewed by occupational hygienists, and grouped according to the major EM frequency range emitted by the source. Exposures to each source were evaluated separately. A slightly increased risk of neuroblastoma was seen among offspring of mothers who worked with RF-emitting equipment ( $OR = 2.8$ ; 95% CI, 0.9–8.7), based on 12 cases, and using exposure data reviewed by industrial hygienists. ORs above 2 were reported for paternal exposures to mobile radio transmitters

or stationary radar use, although overall, fathers' use of equipment emitting power-frequency, RF, or ionizing radiation resulted in ORs much closer to 1 (range 1.2–1.3). Use of cellular phones by mothers was not informative due to the small numbers involved (5 cases); for fathers' use, the OR was 1.1 based on 17 cases, using industrial hygienist assessment of exposure.

Groves et al. (2002) updated an earlier study of Robinette et al. (1980) on mortality related to RF exposure in a cohort of 20,021 Korean War U.S. navy technicians, as compared to other veterans deemed to be in low-exposure jobs. The original study did not find any adverse outcomes related to radar RF exposure; the extended 40-yr follow-up found an overall lower standardized mortality ratio (SMR) and lower risk of death from brain or testicular cancer among the high-exposure as compared to the low-exposure occupations. Death rates for several smoking-related diseases were significantly lower in the high-exposure occupations. Nonlymphocytic leukemia was significantly elevated among men in one of the three high-exposure occupations, namely, electronics technicians in aviation squadrons (SMR = 2.2; 95% CI: 1.3, 3.7). Radar exposure had little effect on mortality in this cohort of U.S. Navy veterans.

This large study with long follow-up does not support the hypothesis that RF exposures result in increased mortality, although the validity of the study results is limited by the use of job title as a surrogate for exposure.

### Epidemiologic Reviews

Elwood (2003) reviewed epidemiological studies of RF fields and cancer. He concludes:

The epidemiological results fall short of the strength and consistency of evidence that is required to come to a conclusion that RF emissions are a cause of human cancer. Although the epidemiological evidence in total suggests no increased risk of cancer, the results cannot be unequivocally interpreted in terms of cause and effect. The results are inconsistent, and most studies are limited by lack of detail on actual exposures, short follow-up periods, and the limited ability to deal with other relevant factors. In some studies, there may be substantial biases in the data used. (p. S63)

A subsequent review by Kundi et al. (2004) focused on nine published studies of mobile phones and cancer, included four studies in the United States (Dreyer et al., 1999; Muscat et al., 2000; Inskip et al., 2001; Muscat et al., 2002), two in Sweden (Hardell et al., 1999, 2001, 2002a, 2002b), and one each from Finland (Auvinen et al., 2002), Denmark (Johansen et al., 2001), and Germany (Stang et al., 2001). Most of these studies focused on brain cancer, although salivary-gland tumors, acoustic neuromas, hematopoietic and lymphatic cancers, intraocular melanomas, and other tumors were also considered. The authors noted that all studies had methodological deficiencies relating to the limited duration of mobile phone use by many target populations, the lack of rigorous exposure measures, and the possibility of recall bias and response error. Nevertheless, it was concluded that "there is evidence for increased cancer risk with increasing latency and duration of mobile phone use" (p. 351).

## NEUROLOGICAL AND BEHAVIOURAL EFFECTS

A number of studies in both humans and animals have examined the possible effects of RF fields on neurological symptoms, cognitive function, electrical brain activity, and neurochemistry. The literature describing these effects is discussed next.

### Human Studies

Table 5 summarizes RF studies on neurology and behavior in humans.

*Neurological symptoms* Sandstrom et al. (2001) conducted an epidemiological study to test whether GSM phones users experience more symptoms than NMT users. In Sweden, 6379 GSM users and 5613 NMT900 users were enrolled, and 2500 from each category in Norway. The adjusted OR did not indicate, for GSM users compared with NMT users, any increased risk for headache, warmth around/behind the ear, or discomfort. However, a statistically significant association

**TABLE 5.** Summary of RF Studies on Neurology and Behavior in Humans

| Reference                    | Type of study   | Exposure   | Results   |
|------------------------------|---|--|---|
| <b>Neurological symptoms</b> |   |  |   |
| Sandstrom et al., 2001       | 6379 GSM users and 5613 NMT900 users in Sweden and 2500 from each category in Norway.             | GSM and NMT900.  | No increased risk for headache, warmth around/behind the ear, or discomfort, for GSM users compared with NMT users. However, a statistically significant association between calling time/number of cells per day and the prevalence headache, discomfort, and warmth was reported. |
| Koivisto et al., 2001        | 48 human volunteers.  | 902 MHz, 217 Hz pulse modulation.  | No subjective symptoms in humans.   |
| Hietanen et al., 2002        | 20 volunteers (13 women and 7 men) who reported themselves as being sensitive to cellular phones. | NMT (900 MHz) and GSM (900 and 1800 MHz); 30 min, and three or four sessions were performed in random order for each subject during 1 d. | Adverse subjective symptoms or sensations, though unquestionably perceived by the test subjects, were not produced by cellular phones.  |
| Navarro et al., 2003         | Survey study in Spain.  | DCS-1800 MHz.  | A significant correlation between the declared severity of symptoms and measured power density.   |
| Santini et al., 2003         | 530 people (270 men, 260 women) living or not in proximity to cellular base stations.             | Cellular base stations.  | Subjective symptoms were experienced significantly more often in the 200 to 300 m zone, as compared to the reference zone 300 m or more from the base stations.   |
| <b>Cognitive function</b>    |   |  |   |
| Lass et al., 2002            | 100 students.   | Hz-modulated 450 MHz; 0.0095 and 0.351 W/kg.   | Decrease in the number of errors for less complicated neuropsychological tasks and an increase in the errors for more complicated ones.   |
| Edelstyn and Oldershaw, 2002 | 38 volunteers.  | 900 MHz; 30 min.   | Significant effect was evident after 5 min on two tests of attentional capacity.  |
| Lee et al., 2003             | 78 volunteers   | GSM; 25 min.   | The results seem to suggest that attention functions may be differentially enhanced after exposing to the RF emitted by mobile phones.  |
| <b>Electrical activity</b>   |   |  |   |
| Lebedeva et al., 2001        | Sleeping humans.  | GSM; 8-h EEG.  | Dimension of EEG correlation dynamics and the relation of sleep stages changed under the influence of GSM radiation.  |
| Jech et al., 2001            | 21 patients.  | 900 MHz, 0.06 W/kg; 45 min.  | RF radiation might enhance performance in subjects with narcolepsy.   |
| Croft et al., 2002           | EEG in 24 human.  | Mobile phones.   | Active mobile phones affect neural function in humans and do so as a function of exposure duration.   |
| Huber et al., 2002           | EEG in human.   | 900 MHz, 1 W/kg; 30 min.   | Exposure to RF fields without pulse modulation did not enhance power in the waking or sleep EEG.  |
| Kramarenko and Tan, 2003     | EEG in human skull.   | Mobile phone radiation concentrated around the ipsilateral eye adjacent to the basal surface of the brain.                               | Mobile phones may reversibly influence the human brain, inducing abnormal slow waves in EEG of awake persons.   |

between calling time/number of calls per day and the prevalence of headache, discomfort, and warmth was reported.

Koivisto et al. (2001) conducted a study on 48 human volunteers. They found that a 30- to 60-min exposure to RF fields from GSM phones (902 MHz with 217 pulse modulation) had no detectable subjective effects such as headache, dizziness, fatigue, itching or tingling of the skin, and sensations of warmth on the skin.

The hypothesis that there exist hypersensitive persons who perceive subjective symptoms from RF fields emitted by cellular phones was tested by Hietanen et al. (2002) using double-blind provocation experiments in Finland. The authors also tested whether sensitive subjects are able to determine whether the phone is on or off by sensing RF fields. The study group consisted of 20 volunteers (13 women and 7 men) who reported themselves as being sensitive to cellular phones. Three different types of phones were used: an analog NMT phone (900 MHz) with an output power of 1 W, and two digital GSM phones operating at 900 and 1800 MHz (pulsed at a frequency of 217 Hz with a pulse width of 577  $\mu$ s) with an average power of 0.25 W and 0.125 W, respectively. The duration of a test session was 30 min, and 3 or 4 sessions were performed in random order for each subject during 1 d. The subjects were asked to report symptoms or sensations as soon as they perceived any abnormal feelings. In addition, the subjects' blood pressure, heart rate, and breathing frequency were monitored every 5 min. The results of the study indicated that various symptoms were reported, and most of them appeared in the head region. However, the number of reported symptoms was higher during sham exposure than during real exposure conditions. In addition, none of the test persons could distinguish real RF exposure from sham exposure. The authors concluded that adverse subjective symptoms or sensations, though unquestionable perceived by the test subjects, were not produced by cellular phones. The single-day multiple cross-over design used by Hietanen et al. (2002) may, however, be subject to certain limitations if RF possibly induces neurological effects that last for longer periods of time (hours).

Navarro et al. (2003) carried out a health survey in Murcia, Spain, in the vicinity of a cellular phone base station working in DCS-1800 MHz. The survey contained items related to "microwave sickness" or "RF syndrome." The microwave power density was measured at the respondents' homes. Statistical analysis showed a significant correlation between the declared severity of symptoms and measured power density.

Santini et al. (2003) administered questionnaires to 530 people (270 men, 260 women) living in proximity or not to BTSSs. Eighteen different nonspecific health symptoms (NSHS), described as RF sickness, were examined. Certain complaints were reported only in the immediate vicinity of BTSSs (up to 10 m for nausea, loss of appetite, and visual disturbances), whereas others were reported at greater distances from BTSSs (up to 100 m for irritability, depressive tendencies, and lowering of libido, and up to 200 m for headaches, sleep disturbances, and feeling of discomfort). Fatigue was experienced significantly more often in the 200 to 300 m zone, as compared to the reference zone 300 m or more from the BTSSs.

*Cognitive function* Lass et al. (2002) performed 3 tests of cognitive function on 100 students. The students were randomly assigned to 2 groups, one of which was exposed to 7 Hz-modulated 450 MHz EM radiation. The SAR was between 0.0095 and 0.351 W/kg, depending on the method used for calculation. The students were unaware of their exposure status. The tests had different degrees of complexity, and measured attention and short-term memory. The authors conclude that 7-Hz modulated microwave radiation has different effects on cognitive tasks of different complexity levels. They state that "these effects might cause a decrease in the number of errors for less complicated neuropsychological tasks and an increase in the errors for more complicated ones" (p. 937).

Edelstyn and Oldershaw (2002) exposed 38 volunteers who were assigned to 2 groups; an experimental that was exposed to a connected mobile phone, and a control group in which the phone was turned off. The experimental group was exposed to 900 MHz from a mobile phone for 30 min. Cognitive performance was assessed prior to mobile phone exposure and at 15 and 30 min postexposure. Significant differences between the two groups were evident after 15 min on 2 tests of attention capacity and one of processing speed. The authors concluded that in all three instances, performance was facilitated following mobile phone exposure.

Lee et al. (2003) randomly assigned 78 volunteers to an experimental or a control group. A GSM phone was mounted to the subject's head during the procedure with the earphone over the right ear. The participants did not know whether the phone was on or off. Two tasks of attention were performed while the phone was on in the experimental group and off in the control group. The subjects were required to complete the tasks within 25 min, and after a 2-min rest the tasks were repeated, but the phone was switched off in both groups. There was no difference between the groups in the reaction times or in the number of correct responses in the first task. Reaction time in both groups significantly improved in the second trial, suggesting a practice effect. In this task, the experimental group improved its reaction time in the second trial significantly more than the controls. The authors suggest that attention functions may be differentially enhanced after exposure to the EM field emitted by mobile phones. Furthermore, this transient facilitation effect might be dose dependent. In the second task, there was no significant difference in performance between the two groups, although both the experimental and the control group improved in the second trial. Previous findings suggested the facilitating effect of the EM field emitted by mobile phones on human attention (Lee et al., 2001; Petrides, 2001).

Haarala et al. (2003) conducted a study to replicate results obtained in a previous study (Koivisto et al., 2000) on effects of the EM fields emitted by a 902-MHz mobile phone on human cognitive functioning, but with methodological improvements. The results of their study indicated that EM fields had no effect on reaction times or on the accuracy of the subjects' answers. They conclude that EM fields had no immediate effect on human cognitive functioning or that such effects are so small that they are observed on behavior only occasionally.

Smythe and Costall (2003) randomly assigned 62 healthy volunteers (33 men, 29 women) to one of 3 experimental conditions: no phone exposure; exposure to 1800-MHz mobile phone (SAR 0.79 W/kg); and inactive phone exposure. They were provided with a series of words to learn, structured in a two-dimensional shape, and given 3 min to memorize the words. After a 12-min distraction task they were then asked to draw the shape (spatial) and place the correct words (semantic) into the appropriate boxes. The results showed that the males exposed to an active phone made fewer spatial errors than those exposed to an inactive phone. The subjects, however, were randomized without reference to gender, and the gender analysis appears to have been post hoc. When the "no phone" group was included in the analysis there was no significant difference in the number of errors. Furthermore, the results were inconsistent. Males had more errors in the spatial recall task, although the results were not statistically significant.

A recent study from the Netherlands has examined the effects of RF signals from mobile phone base stations on feelings of well-being and cognitive functions. Zwamborn et al. (2003) recruited 36 subjects who had reported complaints that they attributed to GSM exposure from base-station antennas. Another 36 subjects without these complaints also participated. Feelings of well-being were assessed by a questionnaire after actual or sham exposure, and cognitive functions were measured during RF exposure. They were exposed to SARs between 0.064 and 0.078 mW/kg at 900 MHz and 1800 MHz by replicating GSM fields, and also the 2100-MHz UMTS (3G) fields. The study found a statistically significant relation between the UMTS fields and feelings of well-being for both the sensitive and the control group. No such effect was seen for the GSM at 900 and 1800 MHz. Some effects were observed also in cognitive function tests but there were a higher number in the control group than the sensitive group, and the pattern of these results is quite variable.

*Electrical activity* In an investigational analysis, Lebedeva et al. (2001) found that when human beings were exposed to the EM field of mobile phones, their cerebral cortex biopotentials revealed an increase in the alpha range power density as compared to the placebo experiment. The dimension of electroencephalogram (EEG) correlation dynamics and the relation of sleep stages changed under the influence of mobile phone exposure.

Jech et al. (2001) reported experiments on subjects with narcolepsy, who fall asleep suddenly in certain situations, mainly during monotonous activities. Twenty-one patients were exposed for 45 min to 900 MHz at SAR of 0.06 W/kg, close to their right ear. No changes were seen on the EEG after this exposure. The authors had postulated that the RF field would produce a hypnotic effect in these patients, but this was not seen. A subgroup was studied while performing a visual task. Some

EEG changes were seen in response to certain visual stimuli. These were mainly seen in the right hemisphere. The reaction time was also shortened by 20 ms in response to target stimuli. The authors suggest that the RF radiation might enhance performance in subjects with narcolepsy.

Croft et al. (2002) measured both resting EEG and phase-locked neural responses to auditory stimuli of 24 human subjects while a mobile phone was either operating or turned off. Mobile phone exposure altered resting EEG, decreasing 1–4 Hz activity (right hemisphere sites), and increasing 8–12 Hz activity as a function of exposure duration (midline posterior sites). Mobile phone exposure also altered early phase-locked neural response, attenuating the normal response decrement over time in the 4–8 Hz band, decreasing the response in the 12–30 Hz band globally and as a function of time, and increasing midline frontal and lateral posterior responses in the 30–45 Hz band. Authors concluded that active mobile phones affect neural function in humans and do so as a function of exposure duration.

Huber et al. (2002) investigated the effect of RF fields versus sham control exposure on waking regional cerebral blood flow and on waking and sleep EEG in humans in two experiments. In the first experiment, positron emission tomography scans were taken after unilateral head exposure to 30 min of pulsed modulated 900 MHz RF field. In the second experiment nighttime sleep was polysomnographically recorded after RF exposure. Pulse-modulated RF exposure increased regional cerebral blood flow in the dorsolateral prefrontal cortex ipsilateral to exposure. Also, nighttime RF exposure enhanced EEG power in the alpha frequency range prior to sleep onset, and in the spindle frequency range during the second phase of sleep. Exposure to RF fields without pulse modulation did not enhance power in the waking or sleep EEG. Huber et al. (2003) further reported an extended analysis to the previous study, as well as the detailed dosimetry of the brain areas, including the assessment of the exposure variability and uncertainties. Compared EEG was initially increased in the 9–14 Hz range in both experiments. No topographical differences with respect to the effect of RF exposure were observed in the two experiments. Even unilateral exposure during waking induced a similar effect in both hemispheres.

Kramarenko and Tan (2003) used a 16-channel telemetric EEG to record changes during exposure of human skull to EM fields emitted by a mobile phone. Spatial distribution of EM fields was especially concentrated around the ipsilateral eye adjacent to the basal surface of the brain. Traditional EEG was full of noises during operation of a cellular phone. Using a telemetric EEG in awake subjects, all the noise was eliminated, and the EEG showed interesting changes: After a period of 10–15 s there was no visible change, and the spectrum median frequency increased in areas close to the antenna; after 20–40 s, a slow-wave activity (2.5–6.0 Hz) appeared in the contralateral frontal and temporal areas. These slow waves lasting for about 1 s repeated every 15–20 s at the same recording electrodes. After turning off the mobile phone, slow-wave activity progressively disappeared; local changes such as increased median frequency decreased and disappeared after 15–20 min. Similar changes were observed in children, but the slow-waves with higher amplitude appeared earlier in children (10–20 s) than adults, and their frequency was lower (1.0–2.5 Hz), with longer duration and shorter intervals. The results suggested that cellular phones may reversibly influence the human brain, inducing abnormal slow waves in EEG of awake persons.

**Case reports** There are quite a number of case reports on the neurological effects of RF radiation. Hocking and Westerman (2001) reported a neurological abnormality in a patient after accidental exposure of the left side of the face to a CDMA mobile phone radiation from a down-powered mobile phone base station antenna. The patient had headaches, unilateral left blurred vision and pupil constriction, unilateral altered sensation on the forehead, and abnormalities of current perception thresholds on testing the left trigeminal ophthalmic nerve.

Hocking and Westerman (2002) reported a case of a 34-yr-old journalist who complained of symptoms associated with use of a mobile phone. Perception threshold testing before and after exposure showed marked changes in the C-fiber nerves of the affected area compared with the opposite side. This case is supportive of a neurological basis for some cases of dysaesthesiae associated with mobile phone use.

Hocking and Westerman (2003) conducted a literature search for case reports and case series regarding peripheral neurological effects of RF radiation, mainly noxious sensations or dysaesthesia.

The collected data revealed that cases have arisen after exposure to much of the RF range. In some cases, symptoms are transitory but lasting in others. After very high exposure, nerves may be grossly injured. After lower exposure, which may result in dysaesthesia, ordinary nerve conduction studies find no abnormality but current perception threshold studies have found abnormalities. Only a small proportion of similarly exposed people develop symptoms.

*Summary of results* Some studies suggest that exposure to RF radiation may affect cognitive function. These include changes in memory tasks, response patterns, and normal sleeping EEG patterns. Other studies have demonstrated improved cognitive function in volunteers exposed to RF radiation in the frequency range of mobile phones. Subjective symptoms such as dizziness, disorientation, nausea, headache, and other unpleasant feelings might be a direct result of RF fields, although such symptoms are very general and may have many other causes.

Wilén et al. (2003) made use of the information about prevalence of symptoms, calling time per day, and number of calls per day from a previous epidemiological study (Sandstrom et al., 2001). They combined it with measurements of the SAR of the specific mobile phone used by each person included in the study just described. Two new exposure parameters were devised: specific absorption per day (SAD) and specific absorption per call (SAC). The results indicated that SAR values  $>0.5$  W/kg may be an important factor for the prevalence of some of the subjective symptoms, especially in combination with long calling times per day.

### Animal Studies

*Cognitive function* Dubreuil et al. (2002) studied the performance of rats using a head-only exposure system emitting a 900-MHz GSM EM field (pulsed at 217 Hz) for 45 min (SAR = 1 and 3.5 W/kg). Two behavioral tasks have been used to demonstrate performance deficits in spatial learning after EM field exposure: a classical radial maze elimination task and a spatial navigation task in an open-field arena (dry-land version of the Morris water maze). The performances of rats exposed for 45 min to 900 MHz (1 and 3.5 W/kg) were compared to those of sham-exposed and cage-control rats. There were no differences among exposed, sham, and cage-control rats in the two spatial learning tasks. In another study aimed at extending these results with more complex spatial learning tasks and a nonspatial task, Dubreuil et al. (2003) reported that mobile phone RF radiation (45 min of head-only exposure to 900 MHz GSM at densities between 1 and 3.5 W/kg) had no effect on spatial and nonspatial memory of rats.

Yamaguchi et al. (2003) suggest that the exposure to a pulsed 1439-MHz TDMA field at levels about 4 times stronger than emitted by mobile phones (SAR of 7.5 W/kg or 25 W/kg for either 1 h daily for 4 d or for 4 wk) does not affect the learning and memory processes in rats when there are no thermal effects.

*Electrical activity* Tattersall et al. (2001) explored the effect of 700-MHz CW RF fields at low intensity on the electrical activity in slices of rat brain from the hippocampus area. The maximum field intensity was calculated to produce a SAR between 0.0016 and 0.0044 W/kg. Changes were noted in the electrical activity of the rat brain slices. These results were seen in the absence of detectable temperature change. The authors state that the hippocampus is important in spatial learning and memory processes.

Marino et al. (2003b) studied the effect of EM field from a cellular telephone on brain electrical activity, using a novel analytical method based on a nonlinear model. The EEG from rabbits was embedded in phase space, and local recurrence plots were calculated and quantified using recurrence quantitation analysis. When the rabbits were exposed to the radiation (800 MHz band, 600 mW) under conditions that simulated normal human use, the EEG was significantly affected in nine of ten animals studied. The effect occurred beginning about 100 ms after initiation of application of the field and lasted approximately 300 ms. In each case, the fields increased the randomness in the EEG. A control procedure ruled out the possibility that the observations were a product of the method of analysis. No differences were found between exposed and control epochs in any animal when the experiment was repeated after the rabbits had been sacrificed, indicating that absorption of radiation by the EEG electrodes could not account for the observed effect. No effect was seen when deposition of energy in the brain was minimized by repositioning the radiating antenna from

the head to the chest, showing that the type of tissue that absorbed the energy determined the observed changes in the EEG. The authors concluded that, in normal use, the fields from a standard cellular telephone can alter brain function as a consequence of absorption of energy by the brain.

**Neurochemical effects** Testylier et al. (2002) observed the neurochemical modification of the hippocampal cholinergic system during and after exposure to low intensity RF fields. The acetylcholine release in the brain of freely moving rats exposed for 1 h during the day to a 2.45-GHz CW RF field (2 or 4 mW/cm<sup>2</sup>) was measured. Rats exposed at 2 mW/cm<sup>2</sup> did not show significant modification in acetylcholine release, whereas those exposed at 4 mW/cm<sup>2</sup> showed a significant 40% decrease in mean acetylcholine release from hippocampus.

### **Neurological Reviews**

During the past few years, there have been inconsistencies in results between experiments due to various experimental protocols and EM exposure characteristics. Major reviews have evaluated the literature on neurological and behavioral effects and reported their findings. For example, Cook et al. (2002) reported that: "The investigation of weak extremely low frequency magnetic field exposure upon human cognition and electrophysiology has yielded incomplete and contradictory evidence" (p. 144).

Hamblin and Wood (2002) reviewed 14 published papers of the effects of mobile phone RF fields on human brain activity and sleep. They concluded that while the studies are inconsistent and comparison between individual studies is difficult, there is some evidence for effects on EEG. They further reported that "current international safety standards do appear to be adequate to minimize the possibility of harm, if the currently reported effects become substantiated" (p. 659).

In another review of the studies of effects of mobile phones on brain function and behavior, Hossmann and Hermann (2003) concluded: "Most of the reported effects are small as long as the radiation intensity remains in the nonthermal range. However, health risks may evolve from indirect consequences of mobile telephony, such as the sharply increased incidence rate of traffic accidents caused by telephony during driving, and possibly also by stress reactions which annoyed bystanders may experience when mobile phones are used in public places" (p. 49).

D'Andrea et al. (2003b) reviewed the literature concerning RF exposure and behavioural and cognitive effects. They conclude:

Reports of change of cognitive function (memory and learning) in humans and laboratory animals are in the scientific literature. Mostly, these are thermally mediated effects, but other low level effects are not so easily explained by thermal mechanisms. The phenomenon of behavioural disruption by microwave exposure, an operationally defined rate decrease (or rate increase), has served as the basis for human exposure guidelines since the early 1980s and still appears to be a very sensitive RF bioeffect. Nearly all evidence relates this phenomenon to the generation of heat in the tissues and reinforces the conclusion that behavioural changes observed in RF exposed animals are thermally mediated. Such behavioural alteration has been demonstrated in a variety of animal species and under several different conditions of RF exposure. Thermally based effects can clearly be hazardous to the organism and continue to be the best predictor of hazard for homo sapiens. Nevertheless, similar research with man has not been conducted. Although some studies on human perception of RF exist, these should be expanded to include a variety of RF parameters. (p. S39)

### **AUTHORITATIVE REVIEWS**

A number of authorities have conducted detailed reviews of the potential health risks associated with exposure to RF fields. The conclusions drawn from each of these reviews are summarized next.

#### **British Medical Association (2001)**

The British Medical Association published a report on mobile phones and health that both summarizes available knowledge about mobile phones and health, and outlines ongoing and planned research in this area. The report concludes: "The most recently published reviews of the literature

have concluded that whilst there are small physiological effects within the existing guidelines, there are no definite adverse health effects from mobile phones or their base stations. However, all the main professional organizations have called for more research to be conducted, since the possibility that RF radiation may cause adverse effects cannot be ruled out on the currently available data. Clearly, there are large gaps in the knowledge that need to be addressed."

#### **Director General of Health of France (Zmirou, 2001)**

An expert group led by Dr. Denis Zmirou prepared a report to the Director General of Health of France concerning state of knowledge and recommendations about mobile phones, base stations, and health. The report concluded: "Scientific data indicates, with comparative certainty, that due to RF exposure from a mobile phone, a variety of biological effects occur (e.g., EEG profile, reaction time, etc.) at energy levels that do not cause any local increase in temperature. However, in the current state of knowledge of these nonthermal effects, it is not yet possible to determine whether they represent a health hazard." The expert group recommended a risk management approach based on the precautionary principle, aimed at reducing public exposure to RF associated with mobile telephony to the lowest possible level compatible with service quality and justified by current scientific data.

#### **European Commission Scientific Committee on Toxicity, Ecotoxicity, and the Environment (CSTEE, 2001)**

The European Commission Scientific Committee on Toxicity, Ecotoxicity, and the Environment (CSTEE) was requested to prepare an update of the opinion of the Scientific Steering Committee (SSC) on health effects of EM fields, dated 1998, which endorsed the guidelines published by the ICNIRP. The CSTEE appointed a Working Group (WG) to evaluate the scientific findings resulting from new investigations. The WG concluded in its report: "The additional information which has become available on carcinogenic and other nonthermal effects of RF and microwave radiation frequencies in the last years does not justify a revision of exposure limits set by the Commission on the basis of the conclusions of the 1998 opinion of the SCC. In particular, in humans, no evidence of carcinogenicity in either children or adults has resulted from epidemiological studies."

#### **Health Council of the Netherlands (2002)**

The Health Council of the Netherlands prepared a report on the potential risks of EM fields from mobile telephones. The report concluded: "The EM field of a mobile telephone does not constitute a health hazard, according to the present state of scientific knowledge." However, the council recommends conducting more research in the Netherlands on the influence of EM fields on cognitive functions. In a significant departure from the conclusions of the Independent Expert Group on Mobile Phones report (IEGMP, 2000), the council does not recommend the application of the precautionary principle concerning nonthermal effects and finds no justification to recommend restriction in the use of mobile phones by children.

#### **Institute of Electrical Engineers Position Statement (IEE, 2002)**

Every 2 yr the Institute of Electrical Engineers (IEE) publishes on the worldwide web its position statement on the biological and health effects of low-level EM fields and radiation principally attributable to power lines, mobile phones, and base stations. In 2002, the IEE Policy Advisory Group on the Biological Effects of Low Level Electromagnetic Fields concluded that there is still no convincing scientific evidence that shows harmful effects of low-level EM fields on humans. This conclusion is the same as that reached in its previous position statement, the last being in May 2000, and has not been changed by the peer-reviewed literature of the past 2 yr.

#### **Swedish Radiation Protection Authority (Boice & McLaughlin, 2002)**

The Swedish Radiation Protection Authority conducted a review of all published epidemiology studies of cellular phone use and cancer since 1996. The authors concluded that "in our view, a consistent picture has emerged from these studies that appear to rule out, with a reasonable degree

of certainty, a causal association between cellular telephones and cancer to date. While the current state of the science is reassuring, ongoing case-control studies being conducted in 13 countries using a shared protocol, and continued follow-up of cohorts of cellular phone users, should provide further evidence regarding any possible carcinogenic effect associated with long-term cellular telephone use."

### World Health Organization

In response to public concerns, the World Health Organization (WHO) established the International Electromagnetic Fields (EMF) Project to assess the scientific evidence of possible health effects of EM fields. Specific studies have been identified to address the problem of localised exposure. The project has established a formal mechanism for reviewing the research results and conducting risk assessments of EM exposure. It is also developing public information materials, and bringing together standards groups worldwide in an attempt to harmonise international exposure standards.

WHO is also conducting a large-scale epidemiology study being coordinated in over 13 countries through the International Agency for Research on Cancer (IARC), an agency of WHO, to identify if there are links between use of mobile phones and head and neck cancers. Further details of the study are described by Cardis and Kilkenny (1999). Field work for the study is expected to be completed by the end of 2003 (WHO, 2000), with final results to be reported following a careful assessment of the data from this important international investigation.

### CONCLUSIONS

The widespread use of devices that emit RF fields, notably wireless telecommunication devices such as mobile phones, has resulted in increased potential for RF field exposure. The potential health risks from RF fields were reviewed in detail by the Royal Society of Canada (1999). At that time, the panel conducting this review concluded that existing RF guidelines were largely protective of human health based on the scientific evidence available at that time, but noted that several RF fields appeared to be associated with certain biological effects of no known clinical significance that required clarification. The panel also made a number of research recommendations, the most important of which was the conduct of a large-scale epidemiologic study of the potential cancer risks from mobile phone use. The results of the ongoing WHO study of mobile phones will provide important new information in this regard (cf. WHO, 2000).

Subsequently, the IEGMP (2000) reaffirmed the conclusions reached by the Royal Society of Canada (1999). All of the authoritative reviews completed within the last 2 yr have concluded that there is no clear evidence of adverse health effects associated with RF fields from mobile phones. The British Medical Association (2001), for example, concluded that "whilst there are small physiological effects within the existing guidelines, there are no definite adverse health effects from mobile phones or their base stations." At the same time, these same reviews support the need for further research to clarify the possible associations between RF fields and adverse health outcomes that have appeared in some reports, including possible associations with brain cancer (Hardell et al., 2002a, 2002b, 2003a, 2003b; Kundi et al., 2004). Research on the biological effects of low-level RF fields (including modulated signals), such as alteration of enzyme activity and transport of ions across cellular membranes, is also encouraged. Given the advances in human functional and molecular brain imaging and mapping methods (Huber et al., 2002), research using these techniques may help to elucidate the functional and anatomical correlates of such biological effects.

The potential health risks of RF fields should be continually reassessed as new research results become available. RF exposure guidelines also need to be updated as new scientific information on RF fields and health risks is generated. Critical evaluations of current research and up-to-date bibliographies on health risk of EM fields have been published recently (Habash et al., 2003a, 2003b; Brodsky et al., 2003).

The authors of the present update of the original Royal Society of Canada review will continue to monitor the scientific literature on RF fields and health, and plan to provide future updates as new scientific information is reported in the literature.

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